

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
6 March 2003 (06.03.2003)

PCT

(10) International Publication Number
WO 03/018004 A3

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(51) International Patent Classification⁷: A61K 31/40,
31/44, C07D 207/06, 207/20, 207/26, 401/04, A61P
25/04, C07D 207/22, 209/96

(21) International Application Number: PCT/US02/27936

(22) International Filing Date: 29 August 2002 (29.08.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/315,530 29 August 2001 (29.08.2001) US

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(81) Designated States (national): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,
CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,
MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG,
SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ,
VN, YU, ZA, ZM, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),
Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE,
ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK,
TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ,
GW, ML, MR, NE, SN, TD, TG).

Declaration under Rule 4.17:

— of inventorship (Rule 4.17(iv)) for US only

Published:

— with international search report
— before the expiration of the time limit for amending the
claims and to be republished in the event of receipt of
amendments

(88) Date of publication of the international search report:
22 May 2003

For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

WO 03/018004 A3

(54) Title: ANALGETIC PYRROLINE DERIVATIVES

(57) Abstract: A method for inducing analgesia and/or inhibiting abuse of abusive substances includes administration of d-methadone metabolites or their structural analogs. The d-methadone metabolites, EMDP and EDDP, and their structural analogs may be incorporated into a suitable pharmaceutical composition for administration to patients. The invention includes the method itself, certain structural analogs, and pharmaceutical compositions for use in accordance with the method.

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INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/40 A61K31/44 C07D207/06 C07D207/20 C07D207/26
C07D401/04 A61P25/04 C07D207/22 C07D209/96

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K C07D A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, EMBASE, BIOSIS, BEILSTEIN Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 3 149 123 A (FREDERICK CAVALLA JOHN) 15 September 1964 (1964-09-15) column 1	1, 3, 4, 6, 13, 15, 16, 18-23, 25, 26, 28-32
X	CAVALLA ET AL.: "Analgetics based on the pyrrolidine ring" J.MED.CHEM., vol. 8, 1964, pages 316-326, XP002228897 table IV, compounds 7, 29, 30, 59, 60, 71, -/--	1, 3, 4, 6, 13, 15, 16, 18-23, 25, 26, 28-32

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

A document member of the same patent family

Date of the actual completion of the international search

28 January 2003

Date of mailing of the international search report

26/03/2003

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, vol. 91, no. 11, 10 September 1979 (1979-09-10) Columbus, Ohio, US; abstract no. 83167, GORCZYCA, MARIA ET AL: "Synthesis and pharmacological properties of 1,3-substituted and 5-substituted 2-pyrrolidinones" XP002228900 abstract & POLISH JOURNAL OF PHARMACOLOGY AND PHARMACY (1978), 30(5), 675-83 ,	1,3,4,6, 13,15, 16, 18-23, 25,26, 28-32
X	US 4 005 103 A (TEULON JEAN-MARIE) 25 January 1977 (1977-01-25) column 1	13,15, 16, 18-23, 25,26, 28-32
X	GB 915 456 A (HERMANN ALBERT BOEHRINGER;WALTER MAYER LIST; ILSE LIEBRECHT; ERNST BOE) 16 January 1963 (1963-01-16) claims; examples	13,15, 16, 18-23, 25,26, 28-32
X	GB 928 007 A (HERMANN ALBERT BOEHRINGER;WALTER MAYER LIST; ILSE LIEBRECHT; ERNST BOE) 6 June 1963 (1963-06-06) claims; examples	13,15, 16, 18-23, 25,26, 28-32
X	POUPAERT ET AL.: "Structure-Activity Relationships of phenytoin-like anticonvulsant drugs" J.MED.CHEM., vol. 27, 1984, pages 76-78, XP002228898 table I	13-16, 18-26, 28-32
X	CHEMICAL ABSTRACTS, vol. 86, no. 7, 14 February 1977 (1977-02-14) Columbus, Ohio, US; abstract no. 37820, BRASE, DAVID A. ET AL: "Comparison of the inhibition of 5-hydroxytryptamine uptake by methadone and its congeners in human platelets" XP002228901 abstract & BIOCHEMICAL PHARMACOLOGY (1976), 25(14), 1684-6 ,	13-16, 18-26, 28-32
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INTERNATIONAL SEARCH REPORT

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	RUI X ET AL: "Synthesis and Analgesic Activity of Epibatidine Analogues" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 6, no. 3, 6 February 1996 (1996-02-06), pages 279-282, XP004135077 ISSN: 0960-894X the whole document	1-32
A	TONDER J E ET AL: "AGONISTS AT THE ALPHA4BETA2 NICOTINIC ACETYLCHOLINE RECEPTORS: STRUCTURE-ACTIVITY RELATIONSHIPS AND MOLECULAR MODELLING" CURRENT MEDICINAL CHEMISTRY, BENTHAM SCIENCE PUBLISHERS BV, BE, vol. 8, 2001 - May 2001 (2001-05), pages 651-674, XP001106484 ISSN: 0929-8673 pages 658, 661	1-32
A	XIAO Y ET AL: "Noncompetitive inhibition of rat alpha3/beta4 neuronal nicotinic acetylcholine receptor (nAChR) function by both enantiomers of methadone, A mu opioid receptor agonist." SOCIETY FOR NEUROSCIENCE ABSTRACTS., vol. 25, no. 1-2, 1999, page 1240 XP009003070 29th Annual Meeting of the Society for Neuroscience.;Miami Beach, Florida, USA; October 23-28, 1999 ISSN: 0190-5295 abstract	1-32
A	GB 1 401 048 A (SANDOZ LTD) 16 July 1975 (1975-07-16) claims	1-32
P,X	XIAO YINGXIAN ET AL: "Blockade of rat alpha3beta4 nicotinic receptor function by methadone, its metabolites, and structural analogs." JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, vol. 299, no. 1, October 2001 (2001-10), pages 366-371, XP002228899 ISSN: 0022-3565 the whole document	1-32

INTERNATIONAL SEARCH REPORT

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Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos.: 13-32
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 13-32

The claims lack clarity with respect to formula II, in which the valency of the nitrogen seems incorrect, and with respect to the tables in claims 5, 11, 17, and 27, which comprise entries for R2 ("=NCH3") not provided in the preceding claims and which comprise an entry "X", which is not defined in the provided formulae.

Moreover, the initial phase of the search revealed for claims 13-32 a very large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which parts of the claim(s) may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT).

For these reasons, a meaningful search over the whole breadth of the claim(s) is impossible. Consequently, the search has been restricted to: applications of compounds as defined based on the described nicotinic receptor blocking activity (see claims 1-12).

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

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INTERNATIONAL SEARCH REPORT

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